III. REMARKS

A. Pending Claims

Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 are pending. The claims of the present application have not been amended in this response.

B. 35 U.S.C. § 112 Rejections

Initially, Applicants acknowledge with appreciation the Examiner's withdrawal of the previous rejection of claims 2, 9, 21-22, 25-26, and 71 under 35 U.S.C. 112, second paragraph.

In the Office Action the Examiner rejected claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71, and 76-81 under 35 U.S.C. § 112, first paragraph, "as failing to comply with the written description requirement."

In making this rejection, the Examiner stated that "[i]n the amendment of 5/9/05 applicant deleted the phrase "about"; however a careful review of the specification does not provide support for this."

It is respectfully submitted that the disclosure of a range including a lower limit of "about 10" does provide literal support for a claimed lower limit of "10" and that one skilled in the art would consider the claimed range literally supported by the original disclosure. The use of the term "about" expands the scope of the term it is describing and "the use of the word 'about' avoids a strict numerical boundary to the specified parameter." *Pall Corp. v. Micron Separations, Inc.*, 36 USPQ2D (BNA) 1225, 1229 (Fed. Cir. 1995). This position supports the conclusion that the specified parameter which is modified by the term "about" is literally supported by such a disclosure.

Therefore, it is respectfully submitted that one of skill in the art would consider the term "about 10" as literally supporting the value of "10" itself.

Further, the CCPA in *In re Wertheim*, 191 USPQ 90 (CCPA 1976) stated that the Patent and Trademark Office has the initial burden of presenting evidence or reasons why persons skilled in art would not recognize in the disclosure, a description of the invention defined by the claims; pointing to the fact that claims reading on embodiments outside the specification's scope satisfies this burden. See *In re Wertheim*, 191 USPQ at 97. In the present application, the Examiner has not met this burden as the claimed range of "10 to about 32 hours" does not read on embodiments outside the specification's scope of "about 10 to about 32 hours".

The CCPA in *In re Wertheim* further stated that with the applicants specification describing a range of 25% - 60% and specific examples of 36% and 50% supported the claimed range of 35% to 60%. See *id.* at 98. The CCPA stated that "the PTO has done nothing more than to argue lack of literal support which is not enough," and "[i]f lack of literal support alone were enough to support a rejection under §112, then the statement of *In re Lukach* [169 USPQ 795], that 'the invention claimed does not have to be described in *ipsis verbis* in order to satisfy the description requirement of § 112 ,' is empty verbiage." *Id.* at 98. (emphasis added). The CCPA further stated that "[t]he burden of showing that the claimed invention is not described in the specification rests on the PTO in first instance, and it is up to the PTO to give reasons why description not in *ipsis verbis* is insufficient." *Id.* (emphasis added).

In the present application, it is respectfully submitted that the Examiner has taken the position that "10" is not supported literally (i.e., *ipsis verbis*) by "about 10" and has not presented any evidence to meet the burden of proof for this position, other than by stating that the disclosure lacks support for the claimed range. However, it is respectfully submitted that persons skilled in art would recognize the disclosure of "about 10" as supporting the value of "10" itself.

In view of the arguments presented above, the Examiner is respectfully requested to remove the rejection of claims 1-13, 18-91, 21-22, 25-29, 31-54, 57-71, and 76-81 under 35 U.S.C. § 112, first paragraph.

C. 35 U.S.C. § 102 Rejections

Initially, Applicants acknowledge with appreciation the Examiner's withdrawal of the previous rejection of claims 1-5, 7-13, 18-19, 21-22, 25-26, 28-29, 33-37, 39, 41, 43, 76-77, and 80 under 35 U.S.C. 102(b) as being anticipated by Cheng et al.

1. Alberts et al.

Claims 1-13, 18, 19, 21, 22, 25-54, 57-71 and 76-81 were again rejected under 35 U.S.C. §102(b) "as being anticipated by Alberts et al. (5,376,383)."

In making the rejection, the Examiner again stated that ". . . although the prior art does not explicitly state the instant functional limitations, it is the examiner's position that the instant functional limitation is inherent since Albert's example 10 provides a release rate over an 18 hour period," and "[t]hus, the T_{max} would inherently fall within [the] instant range." The Examiner further notes that "[t]he recitation of a newly discovered function inherently possessed by the prior art, does not make distinguish it from the prior art," and "it is the applicant's burden to prove otherwise" (citation omitted). In the Office Action, the Examiner suggested that "the applicant provide a Rule 132 declaration that compares the instant invention's Tmax and that of the prior art to rebut the examiner."

This rejection is traversed. Alberts et al. does not teach the claimed Tmax parameters, nor does the reference teach or suggest the claimed dissolution profiles. Example 10, which is cited by the Examiner, merely states that the formulation gave an 85% release over 18 hours and

does not provide any indication or suggestion for correlating a mean time to maximum plasma concentration (T_{max}).

Contrary to the Examiner's allegations, the examples in Alberts are not substantially similar to the general formula presented in Table I of the instant application. Although the claims are not limited by the general formula in Table I, the table shows that a tablet that can be modified to exhibit the claimed pharmacokinetic parameters can contain a) an inner core containing an alkyl ester of a substituted naphthalene, a water swellable polymer, and an osmotic agent and b) an outer coating containing an enteric polymer and a water-insoluble polymer. In contrast, Alberts describes tablets with cores that **do not** contain water swellable polymers (examples 3-7) and tablets that contain drug mixed with a water swellable polymer, but **do not** have an outer coating containing an enteric polymer and a water-insoluble polymer (examples 8-16). Moreover, the exemplified formulations which exhibit the pharmacokinetic data, of the instant claims contain a core, a seal coat, an inner coating containing an enteric polymer, an outer coating containing an enteric polymer and a water insoluble polymer, and an optional overcoat (see examples 5-9 on pages 35-38; pages 40-44; and tables 6-8). Since the formulations described by Alberts are remarkably different from those taught by the present application, one can not say that the reference inherently discloses the pharmacokinetic parameters and dissolution profiles of the claimed controlled release dosage forms. It is noted that the present claims are not limited to the exemplified formulations and that other formulations which exhibit the claimed pharmacokinetic parameters are encompassed by the claimed invention. For example, pages 19 to 24 of the present specification disclose many different types of formulations which can be modified to provide the claimed pharmacokinetic parameters.

To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2D (BNA) 1746, 1749 (Fed. Cir. 1991). "Inherency, however, may not

be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 20 U.S.P.Q.2D (BNA) at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). See also, *In re Rijckaert* 9 F.3d 1531, 28 U.S.P.Q.2d (BNA) 1955 (Fed. Cir. 1993) (reversed rejection, finding inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

Applicants respectfully submit that the Examiner has not met her burden of proof to make an inherency rejection as there is no indication in the Alberts reference that the claimed Tmax of the present invention must be "necessarily present" in the formulations described in the reference. It is further submitted that if one skilled in the art were able to manipulate the formulations of Alberts to achieve a formulation which met the present claimed limitations, one would have to optimize conditions, ingredients and parameters. For example, critical parameters such as compression force, particle size of initial ingredients, and temperature/humidity conditions are not specified in the Alberts reference.

Further, due to the lack of such critical parameters (e.g., compression force, particle size of initial ingredients, and temperature/humidity conditions) in the Alberts reference, Applicants are unable to compare the instant invention's T_{max} and that of the prior art, as suggested by the Examiner. Applicants further submit that it would be unethical for the applicant to conduct human clinical trials for the sole purposes of establishing patentability.

Therefore, as the Alberts reference does not expressly or inherently teach the presently claimed invention, the Examiner is respectfully requested to remove the 35 U.S.C. § 102(b) of claims 1-13, 18, 19, 21, 22, 25-54, 57-71 and 76-81.

D. 35 U.S.C. § 103 Rejections

Initially, Applicants acknowledge with appreciation the Examiner's withdrawal of the following rejections:

withdrawal of the previous rejection of claim 1-13, 18, 19, 21, 22, 25-48, 70-71, 76-77, and 80 over Klimstra et al (5,668,134);

withdrawal of the previous rejection of claims 48-54, 57-69, 78-79, and 81 over Klimstra et al. (5,668,134) in view of Alberts et al. (4,997,658);

withdrawal of the previous rejection of claims 48-50, 58-59, 62-63, 65-66, 68-70, 71, 78-79 over Cheng et al.; and

withdrawal of the previous rejection of claims 1-13, 18, 19, 21, 22, 25-54, 57-71 and 76-81 over Alberts et al. (4,997,658) in view Chen et al. (5,558,879).

1. Chen et al. (5,837,379)

Claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 were again rejected under 35 U.S.C. § 103(a) "as being unpatentable over US patent 5,837,379 to Chen et al." In making the rejection, the Examiner stated that "[i]t is deemed obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Chen et al and include the instant lovastatin in the controlled release dosage form."

This rejection is traversed. Chen et al. is directed to controlled release dosage forms and only incidentally mentions lovastatin, fluvastatin, simvastatin, and pravastatin in an exhaustive list (see column 2, line 51 to column 3, line 11 of Chen et al.) of over one hundred possible agents including various classes of drugs and specific drugs in multiple forms (e.g., salts, esters, etc.). The only data provided in this patent directed to in-vivo results is data directed to dosage forms of nifidepine, which is not in any way related to, e.g., an alkyl ester of hydroxyl substituted naphthalenes. None of the exemplified formulations includes a drug that is an alkyl

ester of hydroxyl substituted naphthalenes, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone an alkyl ester of hydroxyl substituted naphthalenes. Further, there is no statement in Chen et al. relating to T_{max}, and there is no suggestion in Chen et al. that the *in vivo* plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing the alkyl esters of hydroxyl substituted napthalenes. Therefore, there is no motivation in Chen to produce dosage forms of these compounds having the claimed pharmacokinetic parameters. The present application clearly demonstrates the benefits and need for these dosage forms in Table 12, which shows the advantage of a formulation of the present invention (Lovastatin XL) over immediate release Mevacor®, with respect to changes in LDL- cholesterol, HDL-cholesterol, Total Cholesterol, and Triglycerides.

Applicants respectfully submit that one skilled in the art would not be motivated to select the particular claimed agent (i.e., an alkyl ester of hydroxyl substituted naphthalenes) from the large genus disclosed at column 2, line 51 to column 3, line 11 of Chen et al. In support of this position, it is respectfully submitted that with respect to Chen et al., (i) the size of the genus is not sufficiently small as to render each member of the genus inherently disclosed, (ii) the reference does not expressly teach a particular reason to select the claimed agent; and (iii) there is no teaching of structural similarity in the reference. See MPEP 8th Edition, 2nd revision 2144.08 II (A)(4)(A-C). A discussion of these points follows:

(i) The size of the genus is not sufficiently small as to render each member of the genus inherently disclosed

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Some motivation to select the claimed species or

subgenus must be taught by the prior art. See e.g., *In re Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215.

It is respectfully submitted that the size of the possible active agents which can be used in accordance with Chen et al. is sufficiently large as not to inherently disclose each and every individual species (in this case, lovastatin, fluvastatin, simvastatin, and pravastatin) which falls within their broad genus.

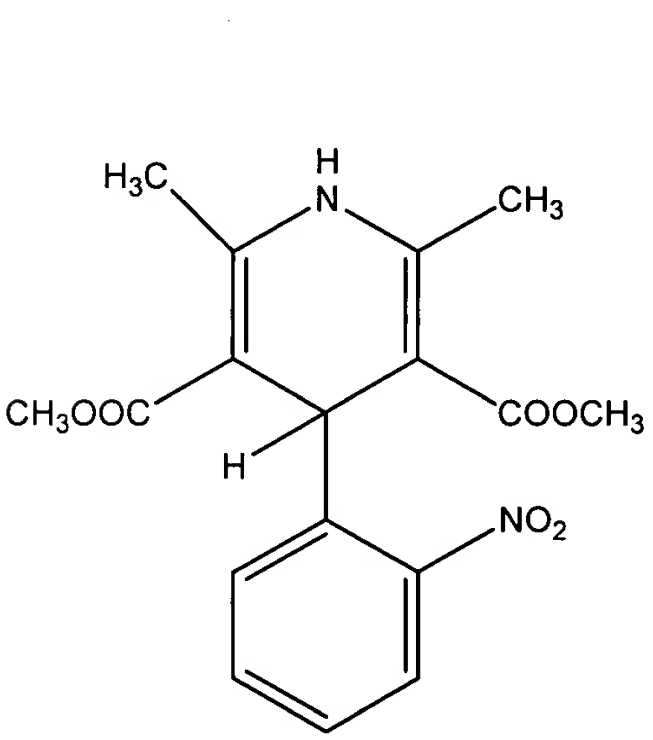
(ii) The reference does not expressly teach a particular reason to select the claimed agent

If a prior art reference expressly teaches a particular reason to select the claimed species, the Examiner should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed species. See MPEP 8th Edition, 2nd revision 2144.08 II (A)(4)(B). It is respectfully submitted that the only recitation of lovastatin, fluvastatin, simvastatin, and pravastatin in Chen et al. is embedded within a large genus. Accordingly, the Chen et al. reference does not expressly teach a particular reason to select an alkyl ester of hydroxyl substituted naphthalenes, such as lovastatin, from the plethora of other possible species in the genus of the reference.

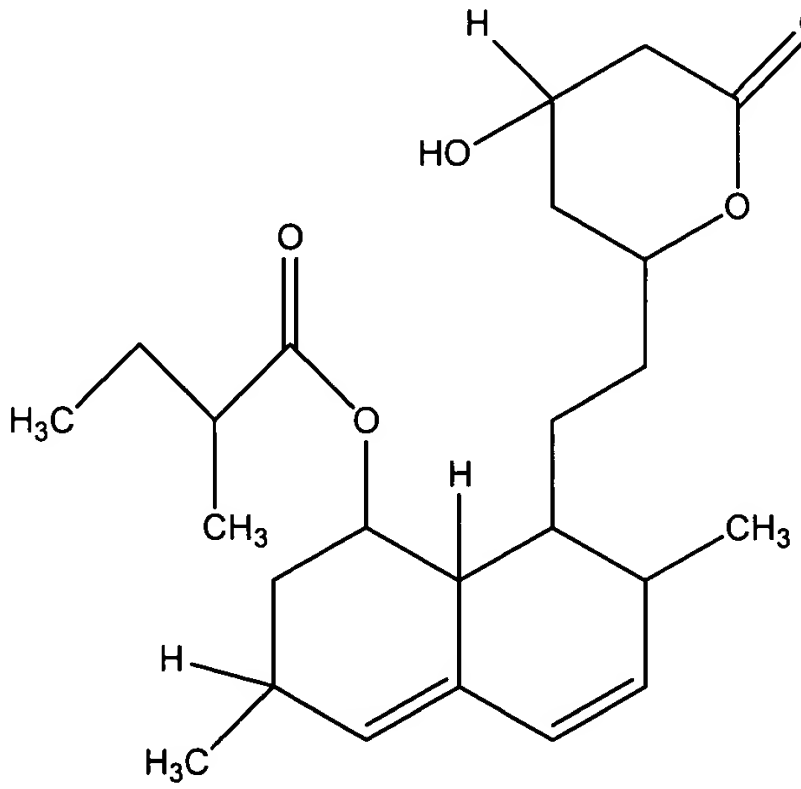
(iii) There is no teaching of structural similarity in the reference

If a preferred species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species from the genus. See, e.g., *In re Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. It is noted that the preferred active agents exemplified in Chen et al. is nifedipine in Examples 1 and 2.

It is respectively submitted that nifedipine is not similar in structure to lovastatin, fluvastatin, simvastatin, and pravastatin (the alkyl esters of hydroxy substituted naphthalenes described in Chen) and does not provide similar pharmacological activity. Nifedipine is a calcium channel blocker which is used primarily for the treatment of hypertension, while lovastatin, fluvastatin, simvastatin, and pravastatin are HMG COA reductase inhibitors for the treatment of hypercholesterolemia. Structurally, nifedipine is a dihydropyridine compound and lovastatin, fluvastatin, simvastatin, and pravastatin are lactone based structures. In order to exemplify, the structures of these lovastatin and nifedipine are set forth below in order to show the dissimilar structures of these agents:



Nifedipine



Lovastatin

Accordingly, as Chen et al. does not teach any preferred species which have structural similarity to lovastatin, fluvastatin, simvastatin, and pravastatin, there is no motivation therein to one skilled in the art to select these agents from the large genus disclosed therein.

Further, any teaching or suggestion in the reference of a preferred species that is significantly different in structure from the claimed species weigh against selecting the later selected species. See, e.g., *In re Baird*, 16 F.3d 382-83, 29 USPQ2d 1552 (Fed. Cir. 1994). Accordingly, the examples of Chen et al. directed to a compound (i.e. nifedipine) that is not structurally similar to lovastatin, fluvastatin, simvastatin, and pravastatin (as discussed above) is further evidence that one skilled in the art would not be motivated to select these compounds from the genus described therein.

Further, the broad ranges described in the present specification at Table 1 provide guidance to one of ordinary skill in the art to prepare a dosage form of the present invention with routine experimentation. One skilled in the art would appreciate that formulations of alkyl esters of hydroxy substituted naphthalenes could be prepared that do not meet the limitations of claim 1, but would generically fall with the ranges of Table 1 of the present application.

Applicants respectfully submit that Chen et al. fail in the very least to teach, hint or suggest the T_{max} range recited in the present claims as no information is provided in the reference concerning a desired time to maximum plasma concentration (T_{max}) for any drug, let alone an alkyl ester of hydroxyl substituted naphthalene. Further, there is no statement in Chen et al. relating to T_{max}, and there is no suggestion in Chen et al. that a particular T_{max} would be desirable for controlled release formulations containing an alkyl ester of hydroxy substituted naphthalene.

Therefore, Applicants respectfully submit that it is only with the benefit of the disclosure of the present application, that one skilled in the art would be motivated to prepare a formulation that provides a time to maximum plasma concentration (T_{max}) as recited in the present claims. Accordingly, the Examiner is using impermissible hindsight reasoning in making this rejection.

Therefore, it is respectfully submitted that Chen et al. do not teach or suggest the presently claimed invention and the Examiner is respectfully requested to withdraw the obviousness rejection over the Chen et al. reference.

E. Double Patenting

Applicants acknowledge with appreciation the Examiner's withdrawal of the double patenting rejection of claims 48-54, 57-71, 78-79, and 81 over U.S. Patent No. 6,485,748; withdrawal of the double patent rejection of the claims over U.S. Patent No. 5,916,595; and withdrawal of the double patenting rejection of claims 48-54, 57-71, 78-79, and 81 over U.S. Patent Application No. 09/435,576.

Claims 1-13, 18, 19, 21, 22, 25-47, 76-77, and 80 were rejected under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claims 1-12 of U.S. Patent No. 6,485,748."

Claims 1-13, 18, 19, 21, 22, 25-47, 76-77, and 80 were also provisionally rejected under the judicially created doctrine of obvious-type double patenting "as being unpatentable over claims of copending Application No. 09/435,576."

1. U.S. Patent No. 6,485,748

The double patenting rejection over U.S. Patent No. 6,485,748 (hereinafter "the '748 patent"), is traversed. Applicants note that when considering when the invention defined in the claim of an application is an obvious variation of the invention defined in the claims of a patent, the disclosure of the patent may not be used as prior art. However, the specification can be used as a dictionary to learn the meaning of a term in the patent claim, or be examined with respect to

those portions which provide support for the claims (See MPEP 8th Edition, Revision 2, Section 804(2)(B)(1)).

It is respectfully submitted that the claims of the '748 patent fail in the very least to teach, hint or suggest the T_{max} ranges recited in the present claims. In addition, there are no dependent claims directed to alkyl esters of hydroxyl substituted naphthalenes or even the general class of HMG CoA reductase inhibitors. In fact, the only dependent claims directed to specific drugs are directed to calcium channel blockers (claims 2 and 3). Furthermore, the specification of the '748 patent, like that of the Chen et al. '379 patent, only incidentally mentions lovastatin, fluvastatin, simvastatin, and pravastatin in an exhaustive list (see column 2, line 58 to column 3, line 16 of the '748 patent) of over one hundred possible agents including various classes of drugs and specific drugs in multiple forms (e.g., salts, esters, etc.). The only *in vivo* data provided in the '748 patent is data directed to dosage forms of nifidepine, which is not in any way related to, e.g., an alkyl ester of hydroxyl substituted naphthalenes, as described above. None of the exemplified formulations includes a drug that is an alkyl ester of hydroxyl substituted naphthalenes, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone an alkyl ester of hydroxyl substituted naphthalenes. Moreover, there is no statement in either the specification or the claims of the '748 patent relating to T_{max}, or suggestion that the *in vivo* plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing the class drugs known as alkyl esters of hydroxy substituted napthalenes.

Applicants respectfully submit that it is only with the benefit of the disclosure of the present application, that one skilled in the art would be motivated to prepare a formulation that provides a time to maximum plasma concentration (T_{max}) as recited in the present claims. Accordingly, the Examiner is using impermissible hindsight reasoning in making this rejection.

Therefore, it is respectfully submitted that the claims of the '748 patent do not teach or suggest the presently claimed invention and the Examiner is respectfully requested to withdraw the obviousness rejection over the '748 patent.

2. Copending Application No. 09/435,576

With respect to the double-patenting rejection of the claims over copending Application No. 09/435,576, Applicants will consider the filing of a terminal disclaimer with respect to this patent and application upon notice from the Examiner that the claims are otherwise allowable.

IV. Conclusion

It is now believed that the above-referenced rejections have been obviated and withdrawal is respectfully requested. It is believed that all claims are now in condition for allowance. According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephone interview will advance the prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,

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